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1,087,842

PATENT SPECIFICATION

NO DRAWINGS

1,087,842

Inventors: KNUT BERTIL HÖGBERG, OVE BIRGER FERNÖ and TORSTEN OVE ENOK LINDEROT

Date of filing Complete Specification: April 30, 1964.

Application Date: May 1, 1963. *No. 17242/63.*

Complete Specification Published: Oct. 18, 1967.

Index at acceptance:—A5 B(1D, 1E, 1F, 1G, 1H, 1M, 1R2, 1S); C4 X11

Int. Cl.:—A 61 k 3/54

ERRATA

SPECIFICATION No. 1,087,842

Page 3, line 19, *for* "are" *read* "as"

Page 6, Example 5, first line, *for* "polyphloretin" *read* "Polyphloretin"

Page 6, Example 6, sixth line, *for* "saccharin" *read* "saccharin"

Page 8, Example 9, first line, *for* "polyphloroglucinol" *read* "Polyphloroglucinol"

Page 9, Example 11, first line, *for* "Polyesperidin" *read* "Polyhesperidin"

Page 9, Example 11, second line, *for* "6,750" *read* "7,650"

THE PATENT OFFICE
20th November 1967

lated compounds) together with a sympathomimetic amine. Compounds of the hydrocortisone group show, however, disagreeable side-effects in the respect that they inhibit the natural defence mechanism of the tissue against infection. Further the duration of the anti-rhinitic effect of such compositions is rather limited. On account of this a composition with the beneficial effects of formerly known decongestive preparations but without their disadvantageous side-effect has been considered highly desirable. We have now surprisingly shown that certain high-molecular weight, antienzymatic compounds show a decongestive effect on the nasal mucosa while at the same time they do not give rise to the undesirable side-effects mentioned above. The decongestive effect is even superior to that obtained with hitherto known compositions. In addition the compositions containing these compounds show a protracted effect superior to previously known compositions. Furthermore, the compounds are non-toxic, especially when administered topically and to nasal mucosa.

[*Price 4s. 6d.*]

in the same nucleus, or

(3) di- or polynuclear aromatic compounds containing at least two different reactive groups on different nuclei,

the said reactive groups being —OH, —SH or —NH_2 groups and the linking to the acid groups of the phosphoric acid being through the polyvalent atoms of the said reactive groups, the said condensation products containing free hydroxy groups linked to the phosphorus atoms of the phosphoric acid groups and being soluble in water at alkaline pH, and

(b) a non-toxic pharmaceutically acceptable carrier therefor.

The high molecular weight anti-enzymatic compound used in the composition of the present invention has a molecular weight of at least 2,000 and not above 50,000, the preferred molecular weight being 2,000 to 25,000.

To further enhance the therapeutic effect 0.1 to 0.5% by weight of a sympathomimetic amine may be present in the composition and, if desired, an anti-biotic may also be included.

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COMPLETE SPECIFICATION

Nasal Decongestive Compositions

We, AKTIEBOLAGET LEO, a Body Corporate organized under the laws of Sweden, of Langvinkelsgatan 166, Halsingborg, Sweden, do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a medicinal composition having particular utility for the treatment of rhinitis. The composition in accordance with this invention has a high degree of decongestive action on nasal mucosas with rhinitic disorders without showing any serious side-effects. The active ingredient provides for a prolonged therapeutic effect.

Compositions with a decongestive effect on nasal mucosas with rhinitic disorders are well-known in the art, e.g. hydrocortisone (and related compounds) together with a sympathomimetic amine. Compounds of the hydrocortisone group show, however, disagreeable side-effects in the respect that they inhibit the natural defence mechanism of the tissue against infection. Further the duration of the anti-rhinitic effect of such compositions is rather limited. On account of this a composition with the beneficial effects of formerly known decongestive preparations but without their disadvantageous side-effect has been considered highly desirable. We have now surprisingly shown that certain high-molecular weight, antienzymatic compounds show a decongestive effect on the nasal mucosa while at the same time they do not give rise to the undesirable side-effects mentioned above. The decongestive effect is even superior to that obtained with hitherto known compositions. In addition the compositions containing these compounds show a protracted effect superior to previously known compositions. Furthermore, the compounds are non-toxic, especially when administered topically and to nasal mucosa.

[*Price 4s. 6d.*]

In accordance with the present invention there is provided a nasal decongestive composition for topical administration comprising:

(a) as the effective nasal decongestive ingredient 0.02% to 2.0% by weight of antienzymatic organic compound having a molecular weight of from 2,000 to 50,000 and which is a condensation product of phosphoric acid with one or more of the following aromatic compounds:

(1) mono-, di- or polynuclear aromatic compounds containing at least two reactive groups in the meta-position to each other in the same nucleus,
(2) mono-, di- or polynuclear aromatic compounds containing at least two reactive groups in the para-position to each other in the same nucleus, or
(3) di- or polynuclear aromatic compounds containing at least two different reactive groups on different nuclei,

the said reactive groups being —OH, —SH or —NH_2 groups and the linking to the acid groups of the phosphoric acid being through the polyvalent atoms of the said reactive groups, the said condensation products containing free hydroxy groups linked to the phosphorus atoms of the phosphoric acid groups and being soluble in water at alkaline pH, and

(b) a non-toxic pharmaceutically acceptable carrier therefor.

The high molecular weight anti-enzymatic compound used in the composition of the present invention has a molecular weight of at least 2,000 and not above 50,000, the preferred molecular weight being 2,000 to 25,000.

To further enhance the therapeutic effect 0.1 to 0.5% by weight of a sympathomimetic amine may be present in the composition and, if desired, an anti-biotic may also be included.

By the term "sympathomimetic amine" is meant the amine itself as well as pharmaceutically acceptable salts thereof. The sympathomimetic agent may be present in the form of a pharmaceutically acceptable organic or inorganic salt, such as the hydrochloride, hydrobromide, phosphate, sulphate, nitrate, acetate, quinate, methanesulfonate, ethanesulfonate, lactate, citrate, tartrate, maleate or pamoate. Other acid addition salts are equally suitable and may be employed if desired. As examples of sympathomimetic amines can be mentioned phenylephrine, methoxamine, cyclopentadrine, naphazoline, tetrahydrozoline, xylometazoline ("Otrivin"), hydroxyamphetamine, cyclopentamine, mephentermine, methylhexaneamine and phenylpropylmethylamine and especially phenylephrine. The word "Otrivin" is a registered Trade Mark. As examples of antibiotics that are useful in the present invention can be mentioned amphomycin, bacitracin, erythromycin, chloramphenicol, neomycin, polymyxin, tetracyclins and tyrothricin. Also other pharmacologically active ingredients such as antihistamines may be added without departing from the spirit of the present invention.

A more detailed description of the production of the high molecular weight, antienzymatic organic compounds used in the composition according to the present invention is given in our British specifications Nos. 700,761, 753,319 and 757,800. They have been recognized as effective antienzymatic agents, e.g. anti-hyaluronidase agents, and this effect has previously been exploited in prolonging the activity of ACTH compositions. Certain of these active agents have also been suggested for use in the treatment of edema of certain types as in the treatment of burns, or in the treatment of peritonitis, in which cases it has been thought to exert an effect upon capillary permeability when applied topically or injected locally. However, to the best of our knowledge, none of these active ingredients have been previously suggested for use in the treatment of nasal congestion or for any method involving application to nasal mucosa or otherwise for use in connection with any rhinitic disorder.

Particularly useful for the composition of this invention are the polymers, the monomer of which is a polyhydroxybenzene with at least two non-adjacent OH-radicals and the polymers: polyphloretin phosphate, polymethylphloretin phosphate, polyquercetin phosphate, polynaringenin phosphate and polyhesperedin phosphate, and the glucosides of these.

Even more particularly useful are polyhesperidin phosphate, polyphloretin phosphate, polyquercetin phosphate and polyphloroglucinol phosphate.

The compositions of this invention may be used for the topical treatment of manifestations of rhinitic disorders of the nasal mucosa which comprises administering from 0.02 to two milligrams, preferably 0.05 to one milligram, of a high molecular weight, antienzymatic organic compound as defined above, either alone or together with 0.1 to 0.5 milligrams of a sympathomimetic amine, together with a non-toxic pharmaceutical carrier or diluent.

Preparations of polyphloretin phosphate alone and polyphloretin phosphate plus sympathomimetic amines have been tested in patients suffering from rhinitis using an objective method of registration. The resistance of a standardized stream of air through the nasal passages was measured in a double blind study in five groups of 18 patients each and the effect was checked by inspection of the mucuous membranes and by interviewing the patients.

Results:

Preparation		Decongestive action			Protracted effect >2 hours in no of cases
		Very good	Good	Slight	
		no of cases			
A.	Polyphloretin phosphate, 0,1%, in water	11	2	5	13
B.	Hydroxyamphetamine HBr 0,5% + phenylephrine HCl 0,125%, in water	—	5	13	0
C.	A + B	11	6	1	16
D.	Polyphloretin phosphate, 0,2% + phenylephrine HCl 0,25%, in water	12	5	1	17
E.	Hydrocortisone 0,02% + B, in water	—	9	9	5

As can be seen, A produced a considerably better decongestive action than B and also a better effect than E. The beneficial effect of the sympathomimetic amines is also clearly indicated in C when compared to A and B.

An additional effect of the solutions containing polyphloretin phosphate was that the tenacious secretions became more fluid, an effect that is considered a therapeutic advantage.

The above-mentioned favourable effects of polyphloretin phosphate have also been clinically confirmed in 300 outpatients.

Because of the non-absorbability of the high-molecular weight, antienzymetic compound, no side effects are likely to occur. Nor have any such side effects been reported in clinical trials.—Similar results are reported above have been obtained with polyphloroglucinol phosphate, polyquercetin phosphate and polyhesperidin phosphate.

The compositions of this invention may be in the form of a solution, preferably an aqueous solution, or a selfpropelled aerosol composition. Exemplary of suitable vehicles are isotonic saline solutions, isotonic dextrose solutions, isotonic buffer solutions and propellants such as lower alkanes and the halogen derivatives of these. For maximum stability of the high molecular weight, antienzymatic compound, the preparation should desirably have a pH of 7.0 or less.

The selected high molecular weight, antienzymatic compound is present in the composition of this invention in an amount of from 0.02% to 2.0% by weight of the preparation and advantageously from 0.05% to 1.0% by weight of the preparation. The sympathomimetic amines and antibiotics may be present in amounts of 0.1 to 0.5% by weight.

The following examples are given by way of illustration of composition of the invention.

EXAMPLE 1

	per cent w/v
Polyphloretin phosphate, sodium salt	0,100
Glycerol	7,650
Ethylenediaminetetraacetic acid, disodium salt	0,100
Sodium citrate	0,100
Saccharin sodium	0,020
Eucalyptol	0,009
Phenylmercuric nitrate, basic	0,001
Ethyl alcohol	0,900
Water q.s. to make total volume of	100 cc

The basic phenylmercuric nitrate is dissolved in water with the aid of a little heat. The ethylenediaminetetraacetic acid disodium salt, sodium citrate and the saccharin sodium are dissolved while cooling, whereupon the polyphloretin phosphate sodium salt is added with stirring. The eucalyptol dissolved in the ethyl alcohol is added followed by the glycerol. The thus mixed ingredients are then filtered and sufficient water added to make the total volume equal to 100 cc.

EXAMPLE 2

	per cent w/v
Polyphloretin phosphate, sodium salt	0,200
Phenylephrine HCl	0,250
Glycerol	7,650
Ethylenediaminetetraacetic acid, disodium salt	0,100
Sodium citrate	0,100
Saccharin sodium	0,020
Eucalyptol	0,009
Phenylmercuric nitrate, basic	0,001
Ethyl alcohol	0,900
Water q.s. to make total volume of	100 cc

The procedure set forth in Example 1 is followed. The phenylephrine HCl is added just before the eucalyptol.

EXAMPLE 3

	per cent w/v
Polyphloretin phosphate, sodium salt	0,050
Phenylephrine tartrate	0,100
Glycerol	7,650
Ethylenediaminetetraacetic acid, disodium salt	0,100
Disodium phosphate 2 H_2O	0,05
Saccharin sodium	0,01
Cyclamate sodium	0,1
Eucalyptol	0,009
Phenylmercuric nitrate, basic	0,001
Ethyl alcohol	0,900
Water q.s. to make total volume of	100 cc

The procedure set forth in Example 2 is followed, the sodium citrate being replaced by disodium phosphate 2 H_2O. The cyclamate sodium is added together with the saccharin sodium.

EXAMPLE 4

	per cent w/v
Polyphloretin phosphate, sodium salt	1,000
Phenylephrine maleate	0,100
Sorbitol	7,650
Ethylenediaminetetraacetic acid, disodium salt	0,100
Potassium biphthalate	0,060
Saccharin sodium	0,020
Menthol	0,008
Thimerosal N.F.	0,001
Ethyl alcohol	0,900

The procedure set forth in Example 2 is followed, the sodium citrate being replaced by potassium phthalate, the basic phenylmercuric nitrate by thimerosal and the eucalyptol by menthol.

EXAMPLE 5

	per cent w/v
polyphloretin phosphate, sodium salt	0,500
Phenylephrine HCl	0,250
Ethylenediaminetetraacetic acid, disodium salt	0,100
Dextrose	4,000
Saccharin sodium	0,020
Eucalyptol	0,009
Phenylmercuric nitrate, basic	0,001
Ethyl alcohol	7,000
Water q.s. to make total volume of	100 cc

The procedure set forth in Example 2 is followed, the sodium citrate being replaced by dextrose and the glycerol being omitted.

EXAMPLE 6

	per cent w/v
Polyphloretin phosphate, sodium salt	0,200
Phenylephrine HCl	0,250
Sorbitol	7,650
Ethylenediaminetetraacetic acid, disodium salt	0,100
Sodium acetate	0,040
Sacchearin sodium	0,020
Eucalyptol	0,009
Phenylmercuric nitrate, basic	0,001
Polyoxyethylene sorbitan monolaurate ("Tween" 20, Atlas)	0,090
Water q.s. to make total volume of	100 cc

The word "Tween" is a Registered Trade Mark.

The procedure set forth in Example 2 is followed, the glycerol being replaced by sorbitol, the sodium citrate by sodium acetate and the ethyl alcohol by "Tween" 20.

EXAMPLE 7

	per cent w/v
Polyphloretin phosphate	0,200
Phenylephrine HCl	0,250
Eucalyptol	0,009
Dipropyleneglycol	20,000
1,2-Dichloro-1,1,2,2, tetrafluoroethane ("Freon" 114) to make total volume of	100 cc

The word "Freon" is a Registered Trade Mark.

The phenylephrine HCl and the eucalyptol are dissolved in the dipropyleneglycol, the polyphloretin phosphate is pulverized and dispersed in the solution. This mixture is then added to the "Freon" 114, which is kept at −25° C, and mixed.

EXAMPLE 8

	per cent w/v
Polyphloretin phosphate, sodium salt	0,100
Phenylephrine HCl	0,125
Hydroxy-amphetamine HBr	0,500
Glycerol	7,650
Ethylenediaminetetraacetic acid, disodium salt	0,100
Sodium citrate	0,100
Saccharin sodium	0,020
Eucalyptol	0,009
Phenylmercuric nitrate, basic	0,001
Ethyl alcohol	0,900
Water q.s. to make total volume of	100 cc

The procedure set forth in Example 2 is followed. The hydroxyamphetamine HBr is added together with the phenylephrine HCl.

EXAMPLE 9

	per cent w/v
polyphloroglucinol phosphate, sodium salt	0,100
Glycerol	7,650
Ethylenediaminetetraacetic acid, disodium salt	0,100
Sodium citrate	0,100
Saccharin sodium	0,020
Eucalyptol	0,009
Phenylmercuric nitrate, basic	0,001
Ethyl alcohol	0,900
Water q.s. to make total volume of	100 cc

The procedure set forth in Example 1 is followed.

EXAMPLE 10

	per cent w/v
Polyquercetin phosphate, sodium salt	0,300
Glycerol	7,650
Ethylenediaminetetraacetic acid, disodium salt	0,100
Sodium citrate	0,100
Saccharin sodium	0,020
Eucalyptol	0,009
Phenylmercuric nitrate, basic	0,001
Ethyl alcohol	0,900
Water q.s. to make total volume of	100 cc

The procedure set forth in Example 1 is followed.

EXAMPLE 11

	per cent w/v
Polyesperidin phosphate, sodium salt	0,500
Glycerol	6,750
Ethylenediaminetetraacetic acid, disodium salt	0,100
Sodium citrate	0,100
Saccharin sodium	0,020
Eucalyptol	0,009
Phenylmercuric nitrate, basic	0,001
Ethyl alcohol	0,900
Water q.s. to make total volume of	100 cc

The procedure set forth in Example 1 is followed.

The high order of activity of the active agents of the present invention and compositions thereof, as evidenced by tests on human beings, is indicative of utility based on their valuable activity in lower animals as well as in human beings. Clinical evaluation in human beings has not yet been completed. It will be clearly understood that the distribution and marketing of any compound or composition falling within the scope of the present invention for use in human beings will of course have to be predicated upon prior approval by governmental agencies, such as the General Medical Council which are responsible for and authorized to pass judgment on such questions.

WHAT WE CLAIM IS:—

1. A nasal decongestive composition for topical administration comprising:

(a) as the effective nasal decongestive ingredient 0.02% to 2.0% by weight of an anti-enzymatic organic compound having a molecular weight of from 2,000 to 50,000 and which is a condensation product of phosphoric acid with one or more of the following aromatic compounds:

(1) mono-, di- or polynuclear aromatic compounds containing at least two reactive groups in the meta-position to each other in the same nucleus,

(2) mono-, di- or polynuclear aromatic compounds containing at least two reactive groups in the para-position to each other in the same nucleus, or

(3) di- or polynuclear aromatic compounds containing at least two different reactive groups on different nuclei,

the said reactive groups being —OH, —SH or —NH_2 groups and the linking to the acid groups of the phosphoric acid being through the polyvalent atoms of the said reactive groups, the said condensation products containing free hydroxy groups linked to the phosphorus atoms of the phosphoric acid groups and being soluble in water at alkaline pH, and

(b) a non-toxic pharmaceutically acceptable carrier therefor.

2. A composition according to claim 1, in which the antienzymatic organic compound is present in an amount of 0.05 to 1.0%.

3. A composition according to either one of claims 1 or 2, in which the anti-enzymatic compound is polyphloretin phosphate.

4. A composition according to either one of claims 1 or 2, in which the anti-enzymatic compound is polyphloroglucinol phosphate.

5. A composition according to either one of claims 1 or 2, in which the anti-enzymatic compound is polyquercetin phosphate.

6. A composition according to either one of claims 1 or 2, in which the anti-enzymatic compound is polyhesperidin phosphate.

7. A composition according to any one of the preceding claims which also includes 0.1 to 0.5% by weight of a sympathomimetic amine.

8. A composition according to claim 7, in which the sympathomimetic amine is phenylephrine.

9. A nasal decongestive composition for topical administration according to claim 1

and substantially as hereinbefore described with reference to the Examples.

STEVENS, LANGNER, PARRY & ROLLINSON,
Chartered Patent Agents,
Agents for the Applicants.

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